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AUTHOR(S):

HORIKOSHI, YUJIRO

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Viral Celiac Ganglionitis as a Possible Etiology of Postoperative Abdominal Neurosis

—Experimental Investigation of Coxsackie B-5 Virus Infection in Monkeys—

by

YUJIRO HORIKOSHI

From the 2nd Surgical Department, Kyoto University, Medical School
(Director : Professor Dr. CHUJI KIMURA)

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I. INTRODUCTION

After laparotomy a few patients suffer from vague abdominal complaints—abdominal pain, obstipation, nausea, vomiting, etc.—which we surgeons cannot ignore. These complaints are mainly psychoneurotic in nature. ARAKI called this syndrome "post operative abdominal neurosis." The pathogenesis is still obscure, although KIMURA[1)-10)] and his coworkers have been investigating the etiology since 1945. Abdominal neurosis develops after laparotomy, especially after appendectomy. In such cases of appendicitis, the inflammatory change in the appendix is usually mild and the main microscopic finding is lymphoid hyperplasia.

TOBE[11)] (1965) demonstrated, by means of a fluorescent antibody technique, Coxsackie B virus antigen or adenovirus antigen mainly in mild appendicitis. BONARD and PACCAUD[12)] (1966) isolated adenovirus from the appendix in such mild appendicitis. Since then viruses, especially enterovirus or adenovirus, have been observed as an etiologic agent in mild appendicitis.

On the other hand, TSENG[13)] (1964) in our department reported that artificial inflammation of both the coeliac lymph plexus and the coeliac ganglion of dogs could be produced lymphogenously by injecting croton oil or phenol solution into the mesenteric lymph nodes of dogs. This study suggested that coeliac ganglion involvement might be caused by an etiologic agent of inflammatory changes in the bowels—neurotropic enterovirus etc.—

However, the pathological aspects of infection with Coxsackie virus or adenovirus have not yet been sufficiently elucidated, although many reports[14)-25)] have been published.

Against this background, the present study was undertaken (1) to elucidate the pathology of infection with Coxsackie B-5 virus (2) to determine whether coeliac ganglionitis as well as meningitis and myelitis can be caused by Coxsackie B-5 virus (3) to clarify the possible etiologic relationship between coeliac ganglionitis and abdominal neurosis and between lymphoid hyperplasia and appendicitis, etc., and (4) to emphasize that the fluorescent antibody technique is a promising one for the pathogenetic study of Coxsackie B virus infection.

II. MATERIALS AND METHODS

Virus

Coxsackie B-5 virus (Furukawa strain) was used in this experiment. The virus was isolated by KONO and HAMADA from the feces and spinal fluid of patients with a mild febrile illness diagnosed as aseptic meningitis in 1960 in Shikoku and has been maintained in the Institute for Virus Research, Kyoto University. Virus for this experiment was prepared in FL cell cultures by HAMADA according to a technique described previously. The virus inoculum had an infectivity of 10^9 50% tissue culture infective dose (TCD_{50}) per ml. on FL cell monolayers and was diluted to an appropriate concentration with Earle's BSS (buffered saline solution) immediately before inoculation.

Monkeys

Eleven healthy cynomolgus monkeys, weighing between 2 and 3 kg., were used in this experiment. Prior to the experiment, they were tested for previous infection with the virus serologically and virologically. All the monkeys' sera showed no neutralizing antibody titres of more than 1 : 2 to the virus, and no virus could be isolated from their throats, fecal and blood specimens before experimental use. Each monkey was kept in a separate cage where it was observed daily for motor activity during the course of the experiment.

Inoculation of the virus

Ten monkeys were inoculated orally through a sterilized polyethylene tube inserted directly into the stomach with 5 ml. of fluid containing 10^9 TCD_{50} of Coxsackie B-5 virus.

Collections of materials

Feces, throat swabs and blood were collected from all the monkeys prior to inoculation and then at daily intervals until the termination of the experiment. Fecal and throat specimens were suspended in Earle's saline. Blood was obtained from the femoral vein and the serum was separated by centrifugation and stored at -20°C until tested for virus or antibody.

At intervals of 1, 2, 5 and 6 days and 1, 2, 3, 4 and 5 weeks, monkeys were sacrificed separately under intravenous Ravonal anesthesia by bloodletting from the carotid artery. The tissues were removed immediately; portions of each tissue were preserved for virus assay; other portions were prepared for immunofluorescent staining and the remainder were fixed in 10% formalin for histopathological examination. As a control, the non-infected monkey was killed and tested in the same way.

Virus isolation

Blocks of tissue and fecal specimens were homogenized with a measured volume of Earle's saline by hand in a tissue grinder, and were set up in ten-fold suspensions. The homogenate was centrifuged at 7,000 rpm for 20 to 30 minutes at 4°C, and 0.5 ml. of the supernatant fluid was poured into roller tubes containing a good monolayer of FL cells. After inoculation, the cultures were incubated at 37°C and were read every other day. The criterion for detection of virus was based on the cytopathic effect (CPE) observed in FL cells cultured in roller tubes. Positive samples were titrated. Each test used a number of control tubes.

Antisera and Immunofluorescent staining methods

The indirect fluorescent antibody technique of COONS and HAMASHIMA was employed in this experiment.

Antiserum (neutralizing titre 1/1,600; used at a dilution of 1/5 to 1/10) prepared in rabbits and goat-antirabbit γ-globulin which had been coupled to fluorescein isothiocyanate were used.

Specimens were prepared from both fresh frozen and the paraffin-embedded tissues and the results of staining were compared. The quality of specific fluorescence was the same in both. However, since better resolution was obtained in pictures of the paraffin-embedded sections, and since the storage of tissues for reexamination was possible only after paraffin-embedding, most the tissues in this experiment were examined after paraffin-embedding.

1) *Staining procedures of frozen section*:

Tissues were placed immediately after removal in glass tubes kept at subfreezing temperatures (−70°C) in an acetone dry-ice bath. Sections were cut (3-4 μ) in a Harris cryostat at −18°C, placed on clean slides, allowed to dry, and then fixed in 95% ethanol for 30 minutes at 37°C. The slides were then washed with phosphate-buffer solution (pH 7.1-7.2) and overlayed with antiserum and incubated for one hour at 37°C in a humidified chamber. The slides were washed again thoroughly with PBS under constant agitation for 15 minutes, overlayed again with the conjugate for one hour, and incubated and washed again with PBS. Then these slides were mounted with 10% buffered glycerol and were covered with coverslips.

2) *Preparation and staining procedures of paraffin-embedded sections*:

As is shown in Table 1, paraffin-embedded sections were prepared and stained very carefully.

A Carl-Zeiss microscope with appropriate ultraviolet light source and filters (−65×41) was used for photomicrography. For photographic records, FUJI colour film for day light (ASA 100) was employed.

The specificity of the staining reaction was confirmed by the following findings: (1) tissues from control animals displayed no fluorescence, (2) there was absence of staining only by the conjugate without antiserum, (3) the staining reaction was absent when the sections of tissues of infected monkeys were treated with monkey antiserum against Coxsackie B-5 virus, followed by application of rabbit antiserum and conjugate, (4) specificity was noted when antiserum was diluted to no higher than 20% concentration, and

Table 1 *Preparation and Staining Procedures of Paraffin-embedded Sections*:

	Fresh specimens					
	↓					
1.	95%	Ethyl alcohol		No. 1	4°C	2 hrs.
2.	〃	〃	〃	No. 2	4°C	12 hrs.
3.	100%	〃	〃	No. 1	4°C	24 hrs.
4.	〃	〃	〃	No. 2	4°C	24 hrs.
5.	〃	〃	〃	No. 3	4°C	24 hrs.
6.	Xylene			No. 1	4°C	10 min.
7.	〃			No. 2	4°C	10 min.
8.	〃			No. 3	4°C	10 min.
9.	Paraffin			No. 1	56°C	5 min.
10.	〃			No. 2	56°C	5 min.
11.	〃			No. 3	56°C	5 min.
12.	Preservation in a cold room.				Cut blocks.	
13.	Xylene			No. 1	room temp.	3 min.
14.	〃			No. 2	〃	3 min.
15.	〃			No. 3	〃	3 min.
16.	99%	Ethyl alcohol			〃	1 min.
17.	95%	〃	〃		〃	1 min.
18.	90%	〃	〃		〃	1 min.
19.	70%	〃	〃		〃	1 min.
20.	45%	〃	〃		〃	1 min.
21.	Wash with cold staining buffer					
22.	Stain					

(5) staining was absent when adenovirus antiserum was used. The greater reliability of these stains was supported not only by appropriate controls in the fluorescent antibody technique, but also by the high coincidence of specific fluorescence with virus isolations from the same tissues; that is, from most of the fluorescence-positive tissues, virus could be isolated.

Hematoxylin-eosin staining and NISSLE's staining were performed as usual with 90% ethanol or 10% formalin fixed sections.

III. RESULTS

In these experiments, 11 monkeys were studied virologically, histo pathologically and immunohistologically. Ten of these were infected with Coxsackie B-5 virus orally and then sacrificed at varying intervals after inoculation; one monkey killed on the seventh day after inoculation developed clinical evidence of incomplete paralysis of the left upper extremity on the fifth day after inoculation. In this monkey, virus was isolate from the cervical segment of the spinal cord, and specific fluorescence was also noted in the meninges of the cervical cord.

The results of virus isolation from feces, throat swabs and blood are summarized in Fig. A.

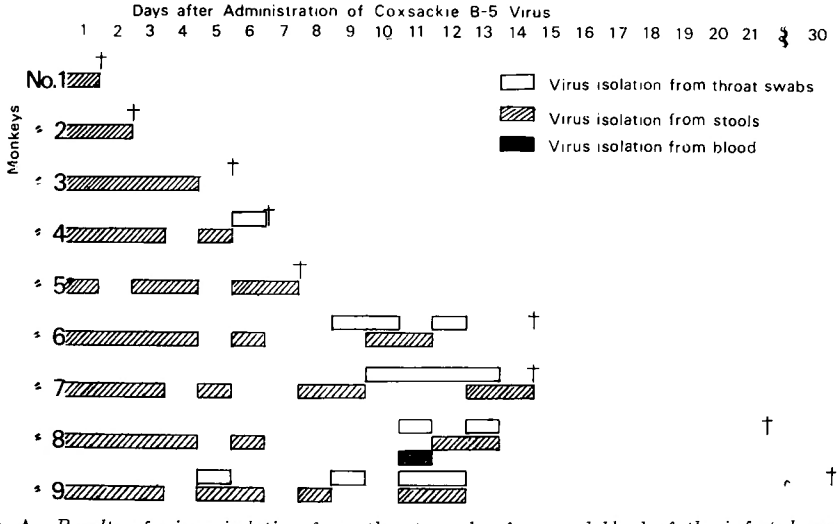

Fig. A *Results of virus isolation from throat swabs, feces and blood of the infected monkeys*

As a rule, virus was recovered from the feces daily up to 5 to 7 days after inoculation; a pause of 4 to 5 days was seen thereafter, and again virus appeared in the fecal specimens for 2 to 3 days. Virus excretion into throat secreta took place concomitantly with the second fecal excretion of virus, 10 to 14 days after infection. Minimal viremia was detected in 9 of the monkeys. A significant rise in neutralizing antibody titre in the animal sera was detected on the 7th day of infection and the titre attained a plateau level of 1 : 124 to 1:248 one month after inoculation.

Table 2 shows that virus was almost always isolated from the distal ends of the ileum 1-14 days and from the spinal cord for 2 to 20 days after inoculation. In addition,

virus was sometimes isolated from the cecum, mesenteric lymph nodes, heart, coeliac ganglion and cerebrum. In contrast, virus was never isolated from the stomach, liver, spleen, kidney or lung.

An attempt was made to visualize Coxsackie B-5 virus antigen in frozen and/or paraffin-embedding sections of infected tissues with immunofluorescent staining methods. The results are shown in Table 3. In addition, histopathological studies were performed on these monkeys.

Table 2 *Results of virus isolation of tissues from the infected monkeys with Coxsackie B-5 virus*

	Control	Days after Administration of Coxsackie B-5 Virus								
		1	2	5	6	7	14	14′	21	30
Stomach	−	−	−	−	−	−	−	−	−	−
Ileum	−	−	+	+	+	+	+	+	−	−
Cecum	−	−	+	+	−	−	−	−	−	−
Mesenteric Lymph Nodes	−	−	+	+	+	−	−	−	−	−
Liver	−	−	−	−	−	−	−	−	−	−
Spleen	−	−	−	−	−	−	−	−	−	−
Lung	−	−	−	−	−	−	−	−	−	−
Heart	−	+	−	−	−	−	+	+	+	−
Kidney	−	−	−	−	−	−	−	−	−	−
Ggl. coeliacum	−	−	−	−	−	−	+	−	+	−
Spinal Cord	−	−	+	+	−	+	+	+	+	−
Cerebellum	−	−	−	−	−	−	−	−	−	−
Cerebrum	−	−	−	+	−	−	+	+	−	−

Table 3 *Results of fluorescent antibody technique of tissues from the infected monkeys with Coxsackie B-5 virus*

	Control	Days after Administration of Coxsackie B-5 Virus									
		1	2	5	6	7	14	14′	21	30	35
Stomach	−	−	−	−	−	−	−	−	−	−	−
Ileum	−	+	+	+	+	+	+	+	−	+	−
Cecum	−	−	+	+	+	+	+	−	−	+	−
Mesenteric Lymph Nodes	−	−	+	+	−	+	−	−	−	−	−
Liver	−	−	−	−	−	−	−	−	−	−	−
Spleen	−	−	−	−	−	−	−	−	−	−	−
Lung	−	−	−	−	−	−	−	−	−	−	−
Heart	−	*	−	+	−	*	*	*	−	−	−
Kidney	−	−	−	−	−	−	−	−	−	−	−
Ggl. coeliacum	−	−	−	−	−	−	+	+	+	−	−
Spinal Cord	−	−	+	+	−	+	+	+	+	−	−
Cerebellum	−	−	−	−	−	−	−	−	−	−	−
Cerebrum	−	−	−	+	−	+	+	−	−	−	−

* The myocardium only was examined ; no pericardium could be examined.

Coxsackie B 5 virus antigen was first detected in the cytoplasm of the crypts of LIEBERKÜHN at the end of the ileum (Fig. 1) on the first day after inoculation, as fine, bright, yellow-green granules. Then, the antigen was demonstrated in the cytoplasm of the epithelium of the ileum villi, in the capillaries in the lamina propria of the villi and in the cytoplasm of the crypts of LIEBERKÜHN in the ileum during the first 2 weeks after infection, and this specific fluorescence lasted up to 3 weeks after infection. One month after infection, the antigen was detected in the cytoplasm of histiocytes in the mucous membrane of the ileum and in the submucosa of the cecum. At this time, hematoxylin and eosin staining showed definite hyperplasia of the lymph follicles in the mucous membrane of the ileum and in the submucosa of the cecum (Fig. 2, 3). Among these findings, the fluorescing histiocytes in the colon epithelium and the hyperplasia of the lymph follicles in the same organ are of special interest in that exactly the same features were observed in human cases of mild appendicitis

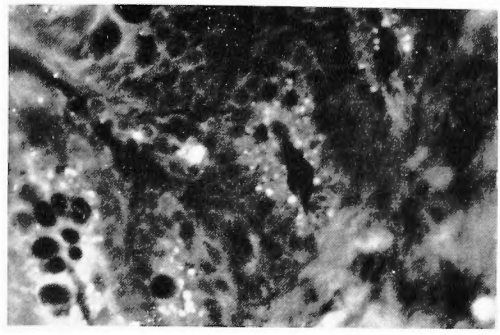

Fig 1

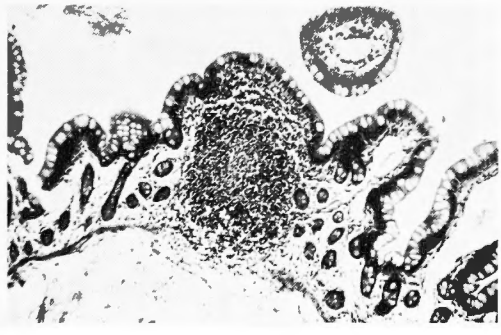

Fig. 2

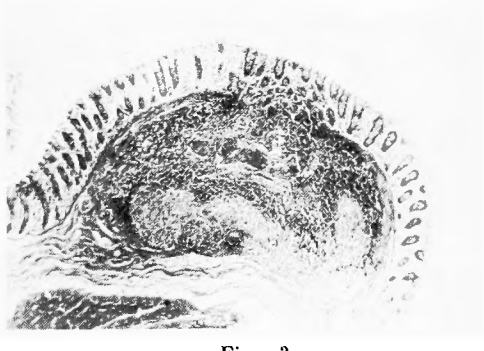

Fig. 3

Specific fluorescence was also detected in the histiocytes in the mesenteric lymph nodes 2 to 7 days after inoculation.

The pericardium was not examined routinely, and fluorescence was detected in only one case on the fifth day after inoculation

Specific fluorescence was never demonstrated in the stomach, liver, spleen, kidney or lung. These results coincided completely with those of virus isolation from the same tissues

In these experiments, the pathologic changes in the coeliac ganglion (visceral sympathetic ganglion) were examined most carefully. In monkeys sacrificed on the 14th day, the cytoplasm of the coeliac ganglion cells contained one or several small aggregates of faintly eosinophilic material encircling the nucleus, and Coxsackie B 5 virus antigen was detected in these materials (Fig. 4, 5). Therefore, these antigen-bearing materials were thought to be cytoplasmic inclusion bodies. In this ganglion, slight round cell infiltration was observed in the perivascular space

In the affected coeliac ganglion of the monkey sacrificed on the 21st day there was involvement of the round cells which showed fairly granular cytoplasmic fluorescence (Fig.

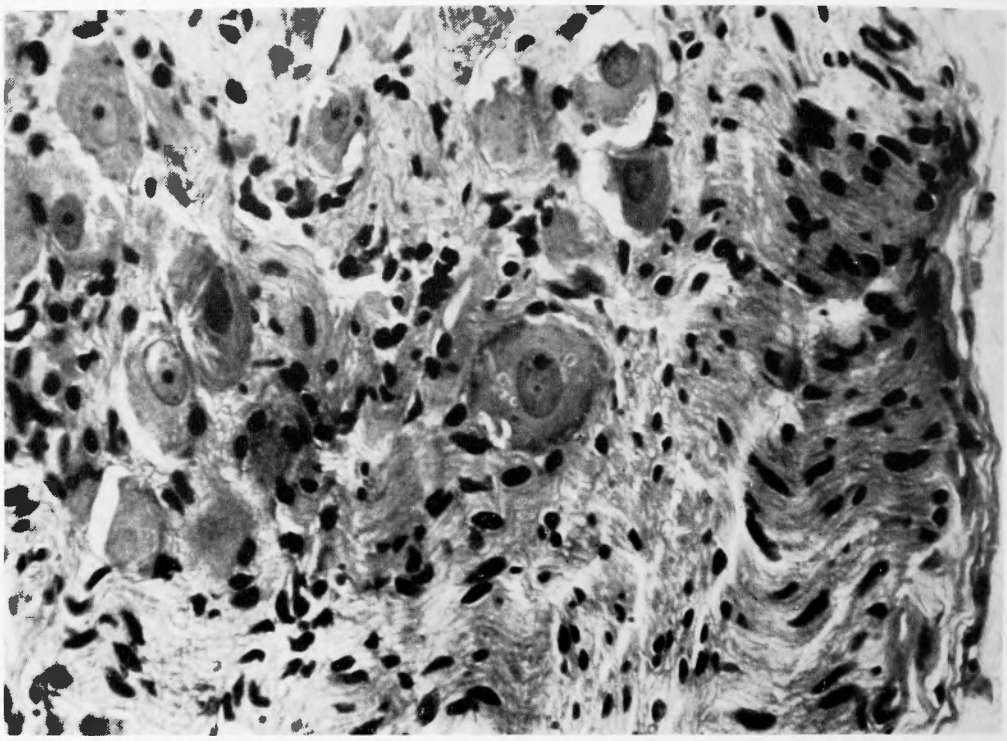

Fig. 4

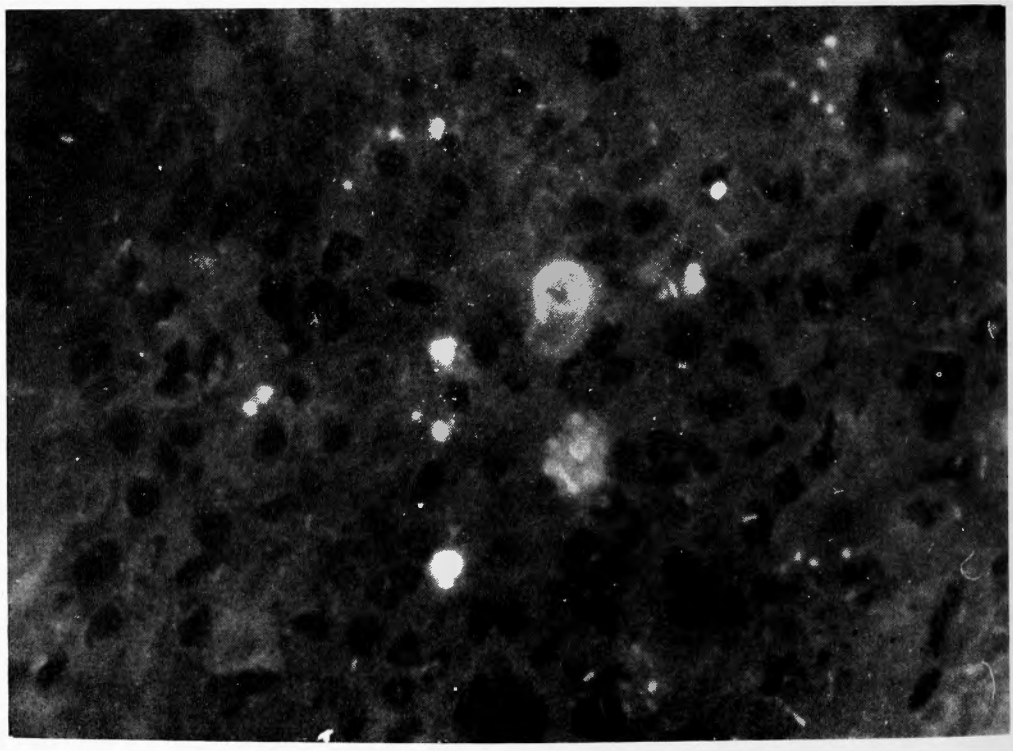

Fig. 5

6). Hematoxylin and eosin staining showed that the antigen-bearing cells around the ganglion cells were mostly round cells with deeply basophilic nuclei. These cells were thought to represent inflammatory components ; that is lymphocytes. Moreover, pathologic changes in the ganglion cells, such as vacuolization and eccentric nuclei, were observed, especially at the pole of the ganglion (Fig 7). These findings showed that coeliac ganglionitis could be caused by Coxsackie B-5 virus.

The spinal cord, cerebrum and cerebellum were examined by means of 4 μ sections stained with immunofluorescent staining, hematoxylin and eosin staining and NISSLE's staining

The Coxsackie B 5 virus antigen was already present in the meninges of the spinal cord on the 2nd day after infection In the cord of the monkey sacrificed on the 5th day a clear picture of leptomeningitis (Fig 8) was noted, and, at the same time, round cell infiltration was observed in the posterior horn of the cord. Coxsackie B 5 virus antigen was detected in the cytoplasm of these round cells (Fig. 9).

By the third week after infection, antigen was noted in the meninges, and antigen-bearing round cells were also seen in the white matter of the cord, especially in the lateral column (Fig. 10). Thereafter the signs of involvement of the spinal meninges disappeared gradually.

On the 21st day after infection granular fluorescence was demonstrated in the cytoplasm of the neurons in the gray matter of the cord (Fig. 11). However, the histopathological findings in the neurons infected with Coxsackie B-5 virus were less severe than in those infected with poliovirus in both H E staining and NISSLE's staining (Fig 12).

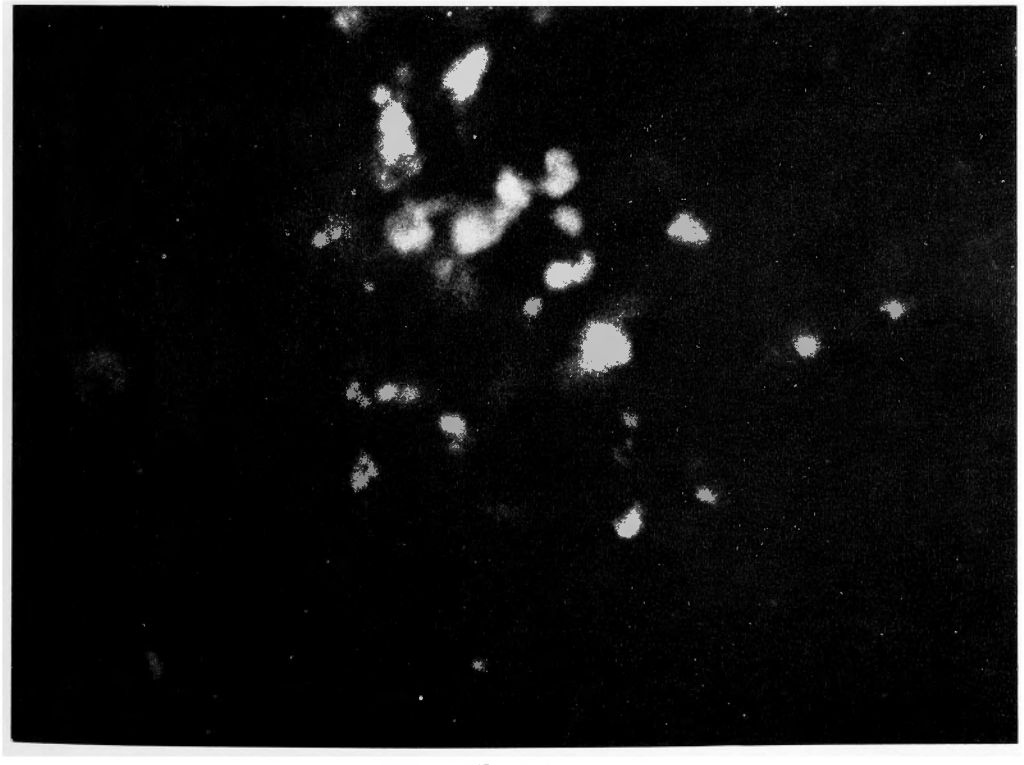

Fig. 6

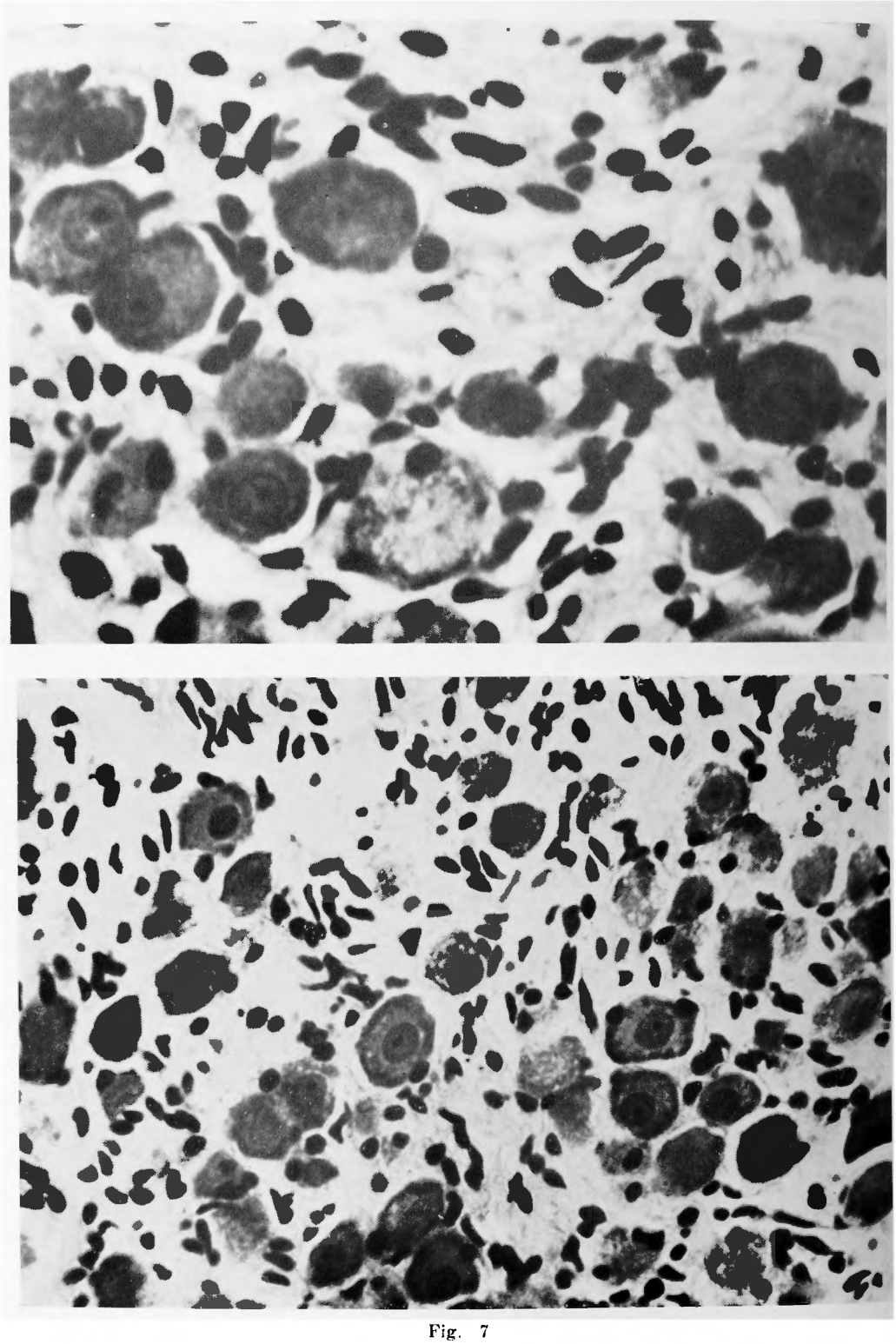

Fig. 7

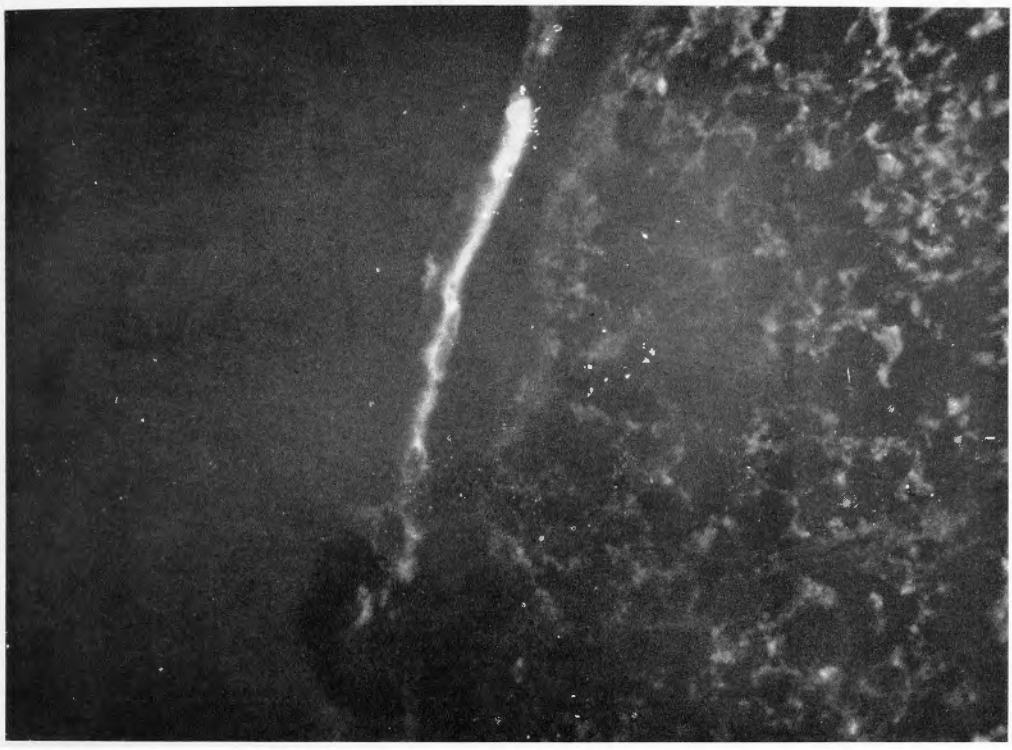

Fig. 8

Fig. 9

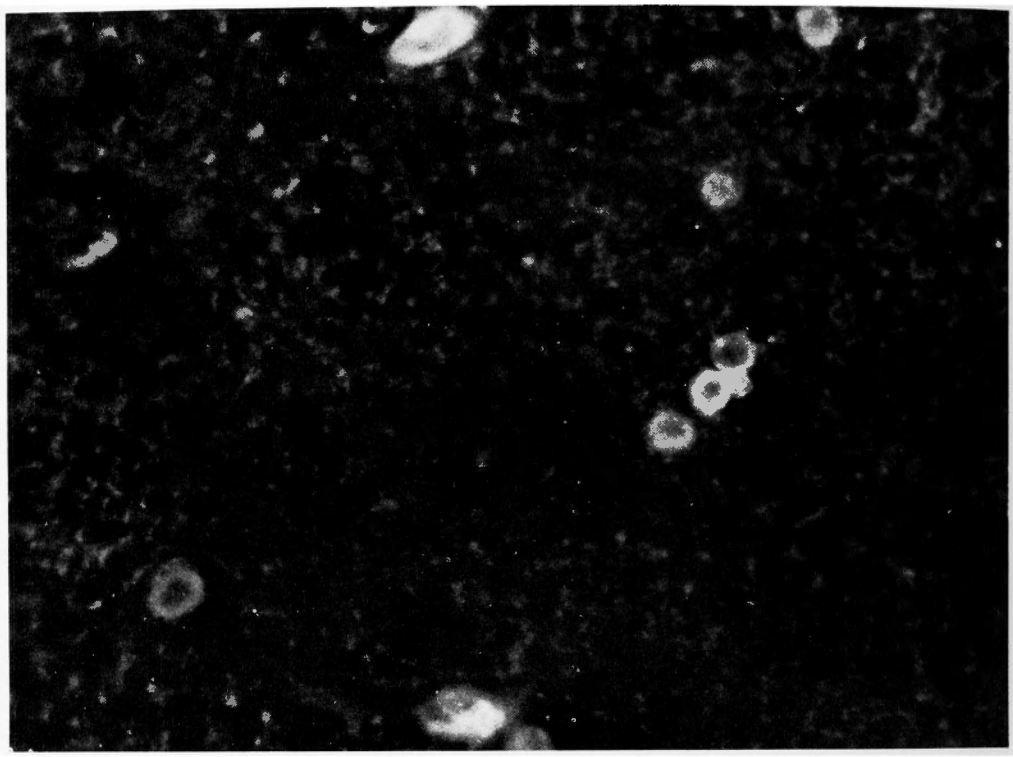

Fig. 10

Fig. 11

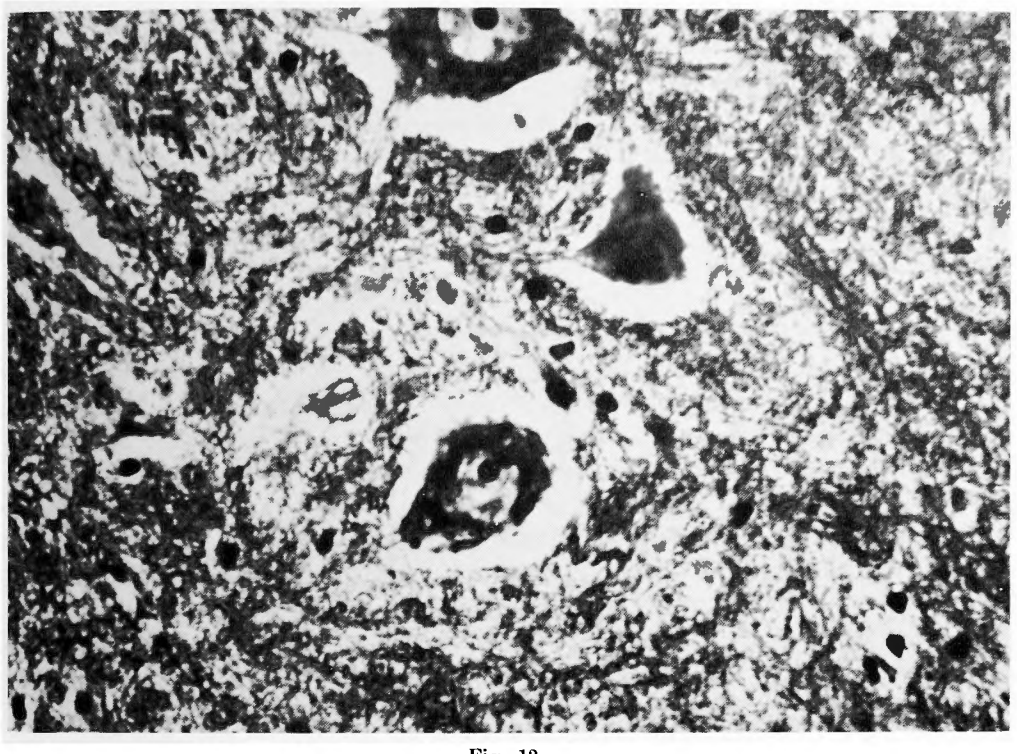

Fig. 12

Specific fluorescence was also detected in the meninges of the cerebrum of monkeys sacrificed from the 5th day to the 2nd week after inoculation. Moreover, the virus could be isolated from all of the fluorescence-positive tissues in the central nervous system.

IV. DISCUSSION

Since the discovery of antibiotics, the symptoms and signs of acute appendicitis have changed significantly. The number of cases of acute suppurative appendicitis that start with epigastric pain which shifts to the ileocecal region accompanied by nausea, vomiting and leucocytosis, and then progress to perforation and peritonitis are decreasing, whereas cases of mild appendicitis are increasing. The main histologic finding in mild appendicitis is lymphoid hyperplasia of the appendix (TOBE et al. 1962), and it is of interest that the appendicitis which leads to abdominal neurosis is usually mild.

With the use of an indirect fluorescent antibody technique, Coxsackie virus (Types B-2 and 5) antigen or adenovirus (Type 7) antigen was demonstrated in the cytoplasm of the macrophages adjacent to the mucous membrane of the appendix, in the cytoplasm of the reticulum cells of the lymph follicles of the appendix, or in the mesenteric lymph nodes (TOBE, 1965). Furthermore, adenovirus has been isolated from the appendix of patients with appendicitis (BONARD et al, 1966). These findings indicate that virus infection plays an important role as a trigger of appendicitis. However, the pathology of Coxsackie B virus infection or adenovirus infection is obscure.

TSENG (1964) reported that celiac ganglionitis could be produced lymphogenously by

injecting chemical agents into the mesenteric lymph nodes in dogs. This fact clearly indicates that symptoms such as epigastric pain, nausea and vomiting in cases of appendicitis can be caused by stimulation of the celiac ganglion.

These findings lead us to consider the following questions: Can enterovirus, especially Coxsackie B virus, or adenovirus cause celiac ganglionitis as well as meningitis and myelitis? Does enterovirus play a role as the causative agent in so-called abdominal neurosis of unknown etiology? Is immunofluorescence reliable in demonstrating enterovirus infection or adenovirus?

In order to simulate the infection in human beings as closely as possible, cynomolgus monkeys were inoculated orally through a polyethylene stomach tube with Coxsackie B 5 virus, and the virus in the tissues and organs was examined immunologically, histologically and virologically. Above all, an experimental model of viral celiac ganglionitis was carefully studied to clarify the pathology of Coxsackie B 5 virus

There are no published records, so far as we are aware, of the visualization of Coxsackie B 5 virus in the nervous system of primates. The neuronal localization and multiplication of Coxsackie B 5 virus has thus been assumed on the basis of histological, biological or clinical findings only. These considerations prompted us to attempt to demonstrate visually, by immunofluorescence, the neuronal localization of the virus.

As we expected two or three weeks after inoculation, celiac ganglion cells showed vacuolization, karyolysis with neuronophagia and the formation of cytoplasmic inclusion bodies containing virus antigen. At this time, the virus could also be isolated in the same ganglion. The findings clearly indicate that celiac ganglionitis can be caused by Coxsackie B 5 virus. The etiologic relationship between celiac ganglionitis and abdominal neurosis will be investigated further. However, it is evident that the final solution of the etiopathogenetic problems of abdominal neurosis cannot be achieved by a simple comparison of the pathomorphological features, but depends on a full knowledge of electrophysiology etc..

The spread of the virus from the site of initial multiplication to the celiac ganglion may occur through several possible routes, of which the most plausible are: (1) neural spread from the site of initial multiplication to the ganglion, (2) centrifugal spread from the cord to the ganglion, and (3) direct invasion from the circulating blood. We did not succeed in isolating the virus from the circulating blood except in one case. The present report provides scant information on the route of virus spread to the celiac ganglion since the number of monkeys available for the examination was limited.

Coxsackie B 5 virus antigen first appeared as early as 24 hr. after inoculation in LIEBERKÜHN'S crypts or in the epithelium of the villi of the terminal ileum, and the virus could be isolated at this time. These findings indicate that the ingested virus initially multiplies in the same regions in the alimentary tract.

The viral antigen was already present in the meninges on the 2nd day after infection. By the third week after infection, antigen was noted in the meninges, and round cells containing viral antigen were also seen in the lateral column. Thereafter, the antigen disappeared from the meninges and was noted in the neurons of the spinal cord. It is of interest that infiltration of round cells containing viral antigen was observed in the posterior horns of the cord on the 5th day after infection. This finding particularly calls

our attention to Coxsackie B-5 virus as a causative agent of pleurodynia. Epidemic pleurodynia was first described by DAAE and HOMANN in 1872, and nearly one-half of the patients with epidemic pleurodynia experienced abdominal pain, with or without chest pain.

The role of these round cells, whether immunological or pathogenic, will be investigated further.

V. SUMMARY AND CONCLUSION

In order to elucidate the pathological aspects of infection with Coxsackie B-5 virus in experimental animals, and in order to investigate the pathological findings in the nervous system, especially in the celiac ganglion, eleven healthy cynomolgus monkeys were inoculated orally through a polyethylene stomach tube with 10^9 TCD_{50} of Coxsackie B-5 virus and then sacrificed at regular intervals. The virus in the tissues and organs of monkeys was examined by indirect immunofluorescent antibody technique with parallel histopathologic observation and by virus isolation from tissue homogenates with FL cells.

As controls, non-infected cynomolgus monkeys were sacrificed and examined.

The results of virus isolation and immunofluorescence showed good coincidence.

The virus antigen appeared as early as 24 hr. after inoculation in LIEBERKÜHN's crypt or in the epithelium of the villi of the terminal ileum, and virus could be isolated at this time. The results suggest that ingested Coxsackie B-5 virus initially multiplies in the mucosal epithelium of the terminal ileum.

In the brain, viral antigen could be detected 5 days to 3 weeks after inoculation.

In the spinal cord, a clear picture of meningitis was indicated in the early stage of infection and later shifted to one of myelitis.

Two weeks after inoculation, celiac ganglion cells showed the formation of cytoplasmic inclusion bodies containing viral antigen. In the monkey sacrificed on the 21st day, there was involvement of round cells containing viral antigen around the celiac ganglion cells. Moreover, degeneration of ganglion cells, such as vacuolization and karyolysis, was observed.

The present study showed that celiac ganglionitis as well as meningitis and myelitis in monkeys can be caused by Coxsackie B-5 virus.

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和文抄録

腹部神経症の一因としてのウィルス性腹腔神経節炎の可能性について

京都大学医学部外科学教室第2講座（指導：木村忠司教授）
堀越雄二郎

腹部神経症の臨床所見或いは電気生理学的実験成果に関しては，既に教室で数多くの業績があるか，腹腔神経節（Ggl. coeliacum）にウィルスが病変を及ぼし得るか否かについて実験的検索を行なつた．即ち，Coxsackie B-5型ウィルス 10^9T. C. D_{50}を，11頭の健常カニクイザル胃内にポリエチレンチューブを用いて接種し，連日，咽頭ぬぐい液，糞便，血液のウィルス分離を試み，血清学的検索と共に，経日的に脱血屠殺し，病理組織学的検索，ウィルス学的検索と同時に螢光抗体法を用いて免疫組織学的研究を行なつた．Coxsackie B-5型ウィルスは，廻腸末端で増殖し，次いで神経系或いは心臓からコンスタントにウィルスが分離され螢光抗体法でもウィルス抗原が確認される．腹腔神経節に於ては，経口接種2週後にウィルス分離陽性で，ガングリオン細胞形質内に明らかに cytoplasmic inclusion body というべき変化を確認し，次いで第3週では変性像を呈する．即ち Viral Ganglionitis とも云い得る変化であり，実験的に Coxsackie B-5型ウィルスのようにありふれたエンテロウィルスが，経口的に感染し，腸管→腸間膜リンパ節→腹腔神経節に病変を及ぼし，所謂腹部神経症の一因となり得ることを示唆する興味のある所見を呈することを確認した．